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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,088	01/18/2007	Zoran Gojkovic	GOJKOVIC3	7165

1444 7590 10/27/2008

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EXAMINER	
KOSSON, ROSANNE	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
10/27/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,088	GOJKOVIC, ZORAN	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-22,26-43,46-50 and 55-75* is/are pending in the application.

4a) Of the above claim(s) *10-15,17,18,21 and 26-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,7,9,16,19,20,22,55,59-63,65-69 and 73-75* is/are rejected.

7)☒ Claim(s) *4,5,56-58,64 and 70-72* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 September 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on September 18, 2008 has been received and entered. Claims 1, 6, 55, 59, 61, 63, and 65 have been amended. No claims have been canceled. Claims 73-75 have been added. As discussed in the previous Office action, claims 10-15, 17, 18, 21 and 26-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Accordingly, claims 1-7, 9, 16, 19, 20, 22, 55-75 are examined on the merits herewith.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

The restriction requirement has been discussed in the previous Office actions of March 31, 2008 and May 19, 2008. Applicant notes in his response that the restriction requirement has not been made final, which has delayed his filing a petition. In view of the discussions of the restriction requirement, the restriction requirement is maintained and is made final. Applicant may file his petition.

Specification

Applicant notes in his Response that the priority information for the instant application was provided in an Application Data Sheet. Accordingly, the objection to the specification for lacking this information is withdrawn.

Drawings

Along with his Response, Applicant has supplied a corrected drawing for Figure 1 that shows the gray areas, the amino acids that Applicant considers to be "semi-conserved" among the four insect deoxyribonucleoside kinases disclosed in the specification. Accordingly, the objection to the drawing is withdrawn.

Claim Objections

Applicants have amended claim 55 to depend from claim 1, rather than withdrawn claim 10. Accordingly, the objection is withdrawn.

Claim Rejections - 35 USC § 112, first paragraph, Written Description

In view of Applicant's amendments to the claims, the written description rejections of claims 1-3, 6, 9, 16, 19, 20, 22, 55 and 59-63 are withdrawn.

Claim Rejections - 35 USC § 112, first paragraph, Enablement

In view of Applicant's amendments to the claims, the enablement rejections of claims 59-62 are withdrawn.

Claims 1-3, 6-7, 9, 16, 19, 20, 22, 55, 63, 65, 66 and 69 are again rejected, and claims 67, 68 and 73-75 are rejected, under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide encoding the polypeptide of SEQ ID NO:2, does not reasonably provide enablement for a polypeptide corresponding to one of the genera listed below:

a) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 85% sequence identity to SEQ ID NO:2 and the complements thereof (one species disclosed, SEQ ID NO:1);

b) polynucleotides encoding a mosquito deoxyribonucleoside kinase or kinase variant that has

85% sequence identity to SEQ ID NO:2 and that decreases at least four-fold the IC_{50} of at least one nucleoside analogue (one species disclosed, SEQ ID NO:1, and only one species of the genus of deoxyribonucleoside kinases that decrease at least four-fold the IC50 of at least one nucleoside analogue is disclosed, SEQ ID NO:2);

c) polynucleotides that hybridize to SEQ ID NO:1 under any conditions (from low-stringency to very high-stringency conditions) when no functional polypeptides need be encoded or under medium stringency conditions when a functional polypeptide (a deoxyribonucleoside kinase) is encoded (one species disclosed, SEQ ID NO:1);

d) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 85% sequence identity to SEQ ID NO:2 and that is C-terminally truncated to any degree (no species disclosed, nor is it disclosed how many amino acids may be deleted with the retention of deoxyribonucleoside kinase activity;

e) [withdrawn]

f) [withdrawn]

g) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 85% sequence identity to SEQ ID NO:2 and that has amino acid substitutions (replacements) at any number of positions at which A, L, I, V, P, M, F and/or W are substituted with any one or more or all of A, L, I, V, P, M, F and/or W with the retention of deoxyribonucleoside kinase activity (no species disclosed);

h) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 85% sequence identity to SEQ ID NO:2 and that has amino acid substitutions (replacements) at any number of positions at which S, T, Y, N, Q and/or C are substituted with any one or more or all of S, T, Y, N, Q and/or C, in addition to any number of substitutions as described in genus (g), with the retention of deoxyribonucleoside kinase activity (no species disclosed);

i) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 85% sequence identity to SEQ ID NO:2 and that has amino acid substitutions (replacements) at any number of positions at which K, R and/or H are substituted with any one or more or all of K, R and/or H, in addition to any number of substitutions as described in genera (g) and (h), with the retention of deoxyribonucleoside kinase activity (no species disclosed);

j) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 85% sequence identity to SEQ ID NO:2 and that has amino acid substitutions (replacements) at any number of positions at which D and/or E are substituted with E and/or D, in addition to any number of substitutions as described in genera (g), (h) and (i), with the retention of deoxyribonucleoside kinase activity (no species disclosed);

k) polynucleotides encoding a mosquito deoxyribonucleoside kinase and having 90% sequence identity to SEQ ID NO:1 (one species disclosed, SEQ ID NO:1); and

l) polynucleotides encoding polypeptides that have at least 85% or 90% or 95% sequence identity to SEQ ID NO:2 and that have no function or that need have no function (no species disclosed).

As a result, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The Wands factors in general and the specifically relevant Wands factors were discussed in the previous Office action.

Claims 65-68 and 73-75 have been broadened to delete the functional limitation that the encoded polypeptide has deoxyribonucleoside kinase activity. The encoded polypeptides encompassed by the claims need have no function at all. The specification does not disclose any such polynucleotides or their encoded polypeptides. The specification does not disclose what to do with mutants of SEQ ID NO:2 that have no function. The specification does not

disclose what to do with mutants of SEQ ID NO:2 that have a function different from that of the polypeptide of SEQ ID NO:2, on the off-chance that the mutations to the polynucleotide sequence impart a different function. Thus, the specification does not teach how to use the claimed invention. Because of the lack of guidance, one would have to experiment unduly and completely on a tedious, random, make-and-test basis to figure out how to use the mutant polynucleotides encoding polypeptides that have no function. One would have to experiment unduly and completely on a tedious, random, make-and-test basis to figure out what, if any, function the mutant polypeptides do have. In view of the breadth of the claims, the lack of guidance, including working or prophetic examples, and the entailed undue experimentation, the claims lack enablement.

Regarding claims 1-3, 6-7, 9, 16, 19, 20, 22, 55 and 63, as previously discussed, for polynucleotides encoding polypeptides having 85% sequence identity to SEQ ID NO:2, even with the functional limitation, 85% identity at the protein level allows up to 37 mutations, and thus only $(.66)^{37}$ X 100% or 2.10×10^{-7}% of random mutants having 85% sequence identity would be active. Consequently, 4.75×10^{6} clones of mutants would have to be screened to identify one clone that produces an active protein. Applicant's Fig. 1 shows a multi-sequence alignment of his SEQ ID NO:2 with three other insect deoxyribonucleoside kinases. But, only three other proteins are compared on the amino acid level, and the specification does not disclose any structure-function relationships for the vast majority of the amino acids that Applicant considers to be conserved (those in black boxes). 21 amino acids are considered to be closest to the substrate, but the substrate binding site and the catalytic site are not indicated. The nuclear import signal has only two conserved amino acids. The P-loop has nine conserved amino acids, but the term P-loop does not appear in the specification. Thus, the function and criticality of the P-loop are not disclosed. As a result, due to the lack of guidance, one of skill in

the art would have to experiment unduly to identify the mutants of SEQ ID NO:1 that encode polypeptides having the activity of SEQ ID NO:2. Therefore, these claims lack enablement.

Regarding claim 69, as previously discussed, 90% sequence identity at the polynucleotide level is different than 90% sequence identity at the polypeptide level. This claim encompasses polynucleotides having 90% sequence identity to SEQ ID NO:1, a feature which corresponds to 10% of the 747 nucleotides of SEQ ID NO:1 being changed, which amounts to up to 74 changes. 74 changes could be up to 74 amino acid changes. Even assuming that about one third of the nucleotide changes are silent (i.e., do not result in an amino acid change), this feature encompasses up to about 50 amino acid changes, which is about 20% of the amino acids. It would be undue experimentation to screen the required corresponding number of clones in order to find one active one, 6.96×10^8 clones of mutants, as previously discussed (and then sequence the encoding DNA in that clone). Therefore, this claim lacks enablement.

Applicant asserts that the claims are limited to a kinase that is "highly similar" to SEQ ID NO:2. Applicant refers to the BPAI's decision in Ex parte: Kubin, to Fig. 1 and to the technique of alanine scanning mutagenesis in support of enablement. Applicant provides an equation, which allegedly is the factor by which the random screening is reduced when one uses the substitutions contemplated on p. 9 of the specification.

In reply, the case of Ex parte: Kubin has no bearing on the instant case. Enablement is very fact-specific, and a set of mutant polynucleotides in one case may be considered to be enabled when they are not in a different case. This case is pending before the CAFC, and, as a result, examiners at the present time have not been instructed to apply anything from Ex parte: Kubin as guidelines for enablement or the lack thereof. Moreover, in the case of the protein of Kubin et al. (NAIL), as discussed in the Board's decision, this protein is not a novel protein and is the same as the p38 of Valiante et al., a protein that has been known and studied since the

early 1980's. Thus, at least some information relating structure and function for the protein was known at the time of the invention of Kubin et al. Screening for active mutants was not random. As discussed above, Fig. 1 provides structural information but very little information for structure related to function. The function of the conserved amino acids is not disclosed, the criticality of an amino acid position that is closest to the substrate is not disclosed, the catalytic and substrate binding sites are not disclosed, and the tolerance of SEQ ID NO:2 to amino acid mutation is not disclosed. Alanine scanning mutagenesis is a known and useful technique. But, the rejection is not that one of skill in the art would not know how to carry out the large amount of experimentation that is required to practice the scope of the claims. The rejection is that this amount of experimentation is undue. As for starting with conservative amino acids substitutions as mutations, one of skill in the art would know to begin his experimentation in this manner, with or without the specification. Such knowledge is common sense to a molecular biologist and is not considered to be Applicant's guidance. As for the claims being limited to kinases highly similar to SEQ ID NO:2, as discussed above, a number of claims do not require that any functional protein be encoded at all. Thus, this feature does not apply to all the claims.

In view of the foregoing, the claims fail to satisfy the enablement requirement.

If, however, the claims were amended to recite that the claimed polynucleotides encode a polypeptide having deoxyribonucleoside kinase activity and having 90% sequence identity to the polypeptide of SEQ ID NO:2, the claims would be considered to be enabled.

Claim Rejections - 35 USC § 112, second paragraph

In view of Applicant's amendments to the claims, the rejections of a polynucleotide derived from a yellow fever mosquito, a complementary strand encoding a protein, the complementary strand encompassing probes and primers (it is now limited to the length of the

coding strand) and hybridization under any unrecited conditions are withdrawn.

Claims 1-3, 9 and 59-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejections related to the previous version of the claims were discussed in the previous Office action. In view of the claim amendments, new rejections are required.

Claims 2-3 recite a kinase that is now compared to the human herpes simplex virus kinase (HSV-TK) (rather to than the virus, as previously recited) when the DNA for the two are transfected into eukaryotic cells. But, as previously discussed, it is unclear what property is compared and how the comparison is a limitation of the claim. Note that, if the claim limitation is intended to be that the presence of the kinase in a cell decreases the IC_{50} of at least one nucleoside analogue by at least 4-fold, this does not in fact require any comparison, particularly to a second kinase. The reduced IC_{50} of the nucleoside analogue (anti-cancer drug) may be due to its phosphorylation. Thus, the phosphorylated form may have a reduced IC_{50} relative to the unphosphorylated form or relative to something else that is not recited in the claim. This limitation is unclear. Appropriate clarification and correction are required.

Claim 59 has been amended to recite the amino acids that are considered to be conserved or semi-conserved, and the claim recites that up to all of the semi-conserved and the non-conserved amino acids may be replaced with the retention of function. But, the claim does not recite the amino acids that Applicant considers to be non-conserved and, therefore, dispensable or mutable. Thus, the meaning of the claim is unclear as its limitations are indefinite. If Applicant's point is that one could figure it out based on the scientific literature and the specification, this laborious, tedious procedure does not amount to clear and definite claim language. Appropriate correction is required.

Claim 61 has been broadened to recite that any or all of the amino acids may be replaced with the retention of function. The claim has been amended to recite the amino acids that are considered to be conserved or semi-conserved, but not non-conserved. Similarly to the above rejection, thus, the meaning of the claim is unclear as its limitations are indefinite. If Applicant's point is that one could figure out the non-conserved amino acids based on the scientific literature and the specification, this laborious, tedious procedure does not amount to clear and definite claim language. Appropriate correction is required.

Claims 60 and 62 have not been amended. They recite the term of amino acid positions that appear at corresponding aligned positions in any other insect kinase. It cannot be determined which other insects and which other insect kinases are referred to. It cannot be determined which positions in SEQ ID NO:2 these amino acid positions are. It cannot be determined which amino acids may be used as the replacements at the "corresponding" positions in SEQ ID NO:2. Appropriate correction is required. The claims may be amended to recite definite amino acid positions in SEQ ID NO:2 that may be replaced with specifically named amino acids that yield a functional deoxyribonucleoside kinase. Alternatively, the claims may be amended to recite that substitutions in SEQ ID NO:2 may be made at corresponding aligned positions in another insect kinase shown in Fig. 1 with the amino acids at those positions that are shown in Fig. 1.

In his response, Applicant describes his claim amendments. The rejections necessitated by the amendments, however, are above. Regarding claims 60 and 62, Applicant asserts that unknown kinases may be sequenced and added to Fig. 1, which would show additional options for mutating SEQ ID NO:2. Applicant refers to Kopchick et al., US 5,958,879, a patent prosecuted by Applicant's representative. In reply, Applicant's claim scope is limited to what he disclosed at the time of filing. Thus, additional sequences may not be added to Fig. 1 to

broaden the claim. As for Kopchick et al., this reference is not on point, because claim 1 in the patent, which is somewhat convoluted and confusing, recites various types of amino acid substitutions relative to two reference sequences. The instant rejection is that the claim recites corresponding aligned positions at other kinases. The other kinases are not disclosed, the alignments are not disclosed, and it is not clear what a corresponding aligned position is.

Claim Rejections - 35 USC § 102

In view of Applicant's amendments to the claims, this rejection is withdrawn.

Claims 4, 5, 56-58, 64 and 70-72 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. In claim 64, it is recommended that the claim be amended to recite that the polypeptide comprises an amino acid sequence identical to SEQ ID NO:2, rather than the current "is characterized by" an amino acid sequence identical to SEQ ID NO:2. The claims should be written to comply with U.S. patent practice.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is (571)272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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rk/2008-10-17

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